# CHAPTER 8

## SUMMARY AND GENERAL DISCUSSION

This thesis studies the associations between physical activity, daily functioning and depression in older people. This knowledge is important for the development of nurse-led interventions aimed at improving functional recovery in late-life depression. To this end, four studies were conducted on a clinical cohort of depressed older subjects participating in the Netherlands Study of Depression in Older persons (NESDO). A total of 378 depressed older patients (≥60 years of age) and a comparison group of 132 never-depressed older persons participated in NESDO.[57] This thesis includes up to two years of prospective data to study the course of late-life depression. In addition, to study the impact of age, we combined data from the NESDO participants with a total of 1701 depressed younger patients (18-65 years of age) who participated in the Netherlands Study of Depression and Anxiety (NESDA) using a similar methodology.[58] The thesis concludes with a systematic review that provides an overview of the impact of antidepressant interventions on functional recovery in late-life depression.

This chapter begins with a brief summary of the main findings of the individual studies. The first three studies, (part 1 of the thesis), focus on the relationship between physical activity and depression, while the last three studies, (part 2 of the thesis), focus on functional recovery from depression. These findings are then integrated into a series of overall conclusions. These conclusions are discussed in the light of the current literature, general clinical implications and direction for further research. This is followed by a discussion of several methodological issues that are relevant to the interpretation of findings from clinical cohort studies, including specific strengths and limitations of our studies. The thesis ends with a description of the clinical implications, primarily from the perspective of the nursing profession.

## Summary of part 1 - Physical activity and late-life depression

In the first part of this thesis, we focus on the association between physical activity and late-life depression. The level of physical activity can be regarded as modifiable factor that is vital for improving physical health conditions and functioning, as well as for reducing depressive symptoms in late-life (see chapter 1). An understanding of the longitudinal relation between physical activity and late life depression is important for the development of lifestyle interventions, but the determinants of physical activity in depressed older patients are still relatively unexplored. Based on cross-sectional analyses, **chapter 2** shows that depressed older patients were less physically active in comparison with their non-depressed counterparts. Adjusted for potential confounders, including demographic, health, cognitive and lifestyle characteristics, this finding remained statistically significant. In the subgroup of depressed older patients, a lower level of physical activity was independently associated with increased functional limitations, a higher number of prescribed drugs, and with inpatient treatment.

**Chapter 3**, explores the predictive contribution of physical activity and sedentary behavior on the depression outcomes at two-year follow-up. Physical activity (total MET/min per week) and sedentary behavior (total sitting min/day) were examined as determinants of late-life depression in multiple regression analyses with models adjusted for cognitive functioning, somatic conditions, psychosocial determinants, and other lifestyle characteristics. In contrast to our hypothesis, we found that in depressed older patients, neither a low level of physical activity nor sedentary behavior was associated with non-remission of the depressive disorder at two-year follow-up or with symptomatic improvement. **Chapter 4** provides possible nuances to these results**.** Chapter 4 examines whether age moderates the reciprocal relationship between physical activity and the course of depressive disorders over two years in patients with depressive disorders. In this study, including a sample of 1079 participants aged 18-93 years, we dichotomized the level of physical activity according to the Dutch guidelines for sufficient physical activity. Fully-adjusted regression models showed that depressed patients with sufficient physical activity at baseline were more frequently in remission at the two-year follow-up compared to depressed patients with insufficient physical activity. This main effect moderated with age. In other words, the association between sufficient physical activity and remission of the depressive disorder at two years decreases with as age increases. Another interesting finding of this study was that the level of physical activity was fairly stable over time; 74 % of the participants had not changed their level of physical activity at follow-up. Only 12 % of the participants switched from insufficient physical activity at baseline to sufficient physical activity at two-year follow-up and 14 % vice-versa. Multinomial logistic regression analyses showed that none of the potential determinants of physical activity (functional limitation, sense of mastery (chapter 3) predicted a change in physical activity over time, irrespective of age and depression outcome (i.e. diagnosis at two-year no/yes or change in IDS score after two years). The relatively low level of physical activity found in our depressed participants may therefore reflect a trait instead of a state characteristic.

## Summary of part 2 - Functional limitations and late-life depression

The second part of this thesis focuses on the relation between functional recovery and late-life depression. Both depression and increasing age are associated with functional decline. Functional disability is increasingly recognized as an important outcome measure in studies on depression, but again, knowledge on the trajectories of functioning in late-life depression is scarce. More insight into the determinants of functional recovery over time could therefore provide new insights into the needs in the treatment and care for older persons with depression. In the NESDO, functional status was measured every six months using the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) self-report. The WHODAS 2.0 is a commonly used interdisciplinary

instrument that contains 36 items, covering six domains of functioning during the last 30 days: 1. Cognition (understanding and communicating); 2. Mobility (moving and getting around); 3. Hygiene, dressing, eating and staying alone (self-care); 4. Interpersonal actions (getting along with people); 5. Work, leisure, domestic responsibilities (household activities); 6. Joining in community activities (participation in society). The items regarding work were omitted for the NESDO study, because most of the participants were retired.

As shown in **Chapter 5**, the 378 depressed older patients had significantly higher levels of functional impairment compared to the 132 never-depressed older persons, as measured with WHODAS 2.0. Based on the semi-annual assessment of functional limitations, we showed that the level of functional limitations remained stable among non-remitted depressed patients and was only slightly improved among remitted depressed patients at a two-year follow-up. Moreover, remitted patients still had far more functional limitations compared to the never-depressed comparison group. The association between depression and functional impairment may suggest that it is important to include a standard clinical assessment of functioning in older subjects with depression, in line with recommendation in the DSM-5 to include measurement of the WHODAS during follow-up of anti-depressant treatment. **Chapter 6** covers the growth mixture modelling that was carried out to explore the existence of different course types of functional limitations among depressed older patients. These analyses yielded two course types, both starting at a high level of functional limitations. The smaller subgroup, consisting of only 1 in 5 depressed older patients, showed a course of functional recovery at the two-year follow-up. The largest subgroup, consisting of 4 out of 5 depressed patients, showed no functional improvement over time. The main predictor of functional recovery was symptomatic remission of depression. Combining these course types with symptomatic remission revealed four groups: 1. a subgroup with symptomatic remission and functional recovery (14 %, most optimal outcome), 2. a group of non-remitted patients without functional recovery (38 %, worst outcome), and two in-between groups consisting of either 3. patients with a symptomatic remission but no functional recovery (31 %) or 4. patients who achieved functional recovery while not being in symptomatic remission (4 %). The remaining participants (13%) were lost to follow up.

Therefore, only 3 out of 10 remitted patients also achieve functional recovery. Interestingly, 1 out of 10 patients with no symptomatic remission did achieve functional recovery. The sample size of this latter group was too small for multivariable analyses, but the finding implies that functional recovery is possible even in the presence of an ongoing, chronic depressive disorder.

Predictors of lack of functional recovery were then explored by multinomial logistic regression, stratified by symptomatic remission yes/no. We found that patients who remained depressed and showed no functional recovery were characterized by the

presence of more chronic somatic diseases, a lower sense of mastery, and higher levels of anxiety, when compared to patients with the most optimal results (reference group). Among symptomatic remitted patients, the lack of functional recovery was associated with female gender, higher educational level, higher gait speed, and lower depressive symptom severity.

Since only 20% of depressed older patients overall were found to achieve functional recovery over a two-year period, we argue that the outcome of mental health interventions should include functional recovery in addition to symptomatic remission.

**Chapter 7** therefore covers that systematic review that was carried out to evaluate the effectiveness of interventions on functional limitations in patients with late-life depression. The 14 randomized controlled trials that were identified by the literature search evaluated four different treatment strategies, i.e. psychological interventions (n=7), pharmacotherapy (n=3), physical exercise (n=3), and collaborative care (N=4). Whereas all of these treatment strategies showed improvement with respect to depressive symptoms, collaborative-care interventions had the most favorable effect on the reduction of functional limitations in late-life depression. To optimize anti-depressant treatment by improving functional recovery, collaborative or integrated care should be the core when treating late-life depression.

## Main findings of the thesis

Since the primary objectives of this thesis are discussed extensively in the separate chapters, this section discusses the four main conclusions based on the different studies. First, we found that the effect of sufficient physical activity on the course of late-life depression remains ambiguous. Second, physical activity seems to reflect a trait rather than a state in late-life depression (and probably at all ages). Third, symptomatic remission of depression does not imply functional recovery in late-life depression. This leads to a fourth conclusion, namely that integrated care is needed for full recovery from late-life depression, and future research should focus on recovery of daily functioning instead of the severity of depressive symptoms only. These four main conclusions will be discussed in more detail below.

### The impact of physical activity on the course of late-life depression: enough is enough?

Sufficient physical activity is associated with improved physical health as well as mental health. Likewise, this thesis confirmed that depressed older patients are less physically active than their non-depressed counterparts (chapter 2). Sufficient physical activity can thus be seen as a protective factor for not developing depressive disorder.[248,249] In this

section, we will argue that sufficient physical activity may also be seen as a predictive factor for remission of depression in clinically depressed patients of all ages. We also discuss that the impact of physical activity on the course of late-life depression remains ambiguous regarding the contradictory results in chapter 3 and 4.

While in chapter 3 no effect of physical activity on late-life depression outcome could be demonstrated, in chapter 4, insufficient physical activity was found to predict an adverse outcome of depression in both younger and older patients. However, this effect was more pronounced in the younger compared to the older age group (chapter 4). The most likely explanation for this contradictory finding in late-life depression is the fact that physical activity was operationalized in two different ways, i.e. total amount of physical activity in MET-minutes in chapter 3 and a dichotomization of physical activity according to the WHO-definition of "sufficient" physical activity.[77] It is important to note that sufficient physical activity is not simply the application of a cut-off on the number of MET-minutes, because the relative contribution of light, moderate and heavy physical activity also has to be taken into account. To examine the discrepant findings in chapter 3 and 4, in chapter 4, we conducted post-hoc sensitivity analyses with the total amount of physical activity (as in chapter 3). These sensitivity analyses showed that a higher total MET-minutes/week at baseline increased the odds of remission at follow up, but in line with chapter 3, this effect was lost in the fully adjusted model and was not moderated by age.

Apparently, the predictive effect of physical activity on remission of depression is characterized by a subthreshold - 'enough is enough' - and not a dose-response relation. Once the level of sufficient physical activity is reached, additional activity does not have an additional effect on depression. This suggests that increasing the level of physical activity from insufficient to sufficient might be helpful in the treatment of depression. This finding is in line with studies in younger depressed patients, in which it was demonstrated that the protective effect of additional exercises is found among persons with relatively low levels of physical activity, with no indication of any additional benefit beyond a certain amount of physical activity a week.[250,251]

The absence of any effect of physical activity on depression outcomes in chapter 3 may also be explained by a lack of statistical power. The strength of this association decreases with age, which implies that a higher number of subjects is needed to demonstrate a statistically significant effect. Nevertheless, patient numbers were markedly lower in the higher age-ranges. Lastly, this age effect may also be explained by the fact that older patients with depression have more pre-existing chronic diseases[165] and the additional high level of functional limitations improves only minimally after remission of the depressive disorder in older people (chapter 5). A course with functional recovery was found in only one fifth of the older patients (chapter 6). The presence of these functional limitations in later life could also explain why improving physical activity can be more difficult in later life.

In conclusion, older subjects with late-life depression have mostly adapted to a lifestyle with a low activity level that is hard to change, partly due to physical inabilities. It is likely that insufficient physical activity predisposes them to developing of depression, and when depressed, sufficient physical activity could lead to a favorable course of depression.

## physical activity in late-life depression reflects a trait rather than a state characteristic

Physical activity is regarded as a key factor with respect to modifiable behavior to improve physical and mental health. Nevertheless, this section argues that physical activity primarily reflects a trait characteristic of depressed patients rather than a state-effect due to the depressive disorder. This statement unfortunately implies that physical activity behavior will be hard to change in late-life depression.

Contrary to our expectations, the level of physical activity hardly changed over time (chapter 4) and this was independent of depression outcome. Neither remission of the depressive disorder, nor a decline in depressive symptoms over time predicted a change in physical activity at follow-up. In the case of a state-effect of the depressive disorder on the level of physical activity, one would expect a dose-response effect. However, the severity of the depression was not associated with the level of physical activity (chapter 2). These findings suggest that the lower level of physical activity found among depressed patients compared to their never-depressed counterparts merely reflects a trait characteristic. This interpretation offers an explanation for the fact that although lifestyle interventions are feasible and may look attractive because they target potentially modifiable behavior, results until now have been rather meager. Physical exercise interventions thus far have only demonstrated marginal short-term effects in the treatment of depression in adults and older adults.[252,253] Thus far, a long-term effect of exercise interventions on depression has not been found.[41] It is important to note that, adherence has been identified as an explanatory factor for the heterogeneity of results of the effect of exercise programs on depressive symptoms by meta-regression analysis of RCT's in late life depression.[252] In other words, high adherence to exercise is a prerequisite for the effectiveness of such lifestyle interventions in reducing depressive symptoms.[254] If the level of physical activity indeed reflects merely a trait rather than a state characteristic, it remains questionable to what extent older adults (with depressed mood) are capable of long-term, sustainable behavioral change with high adherence.

## Symptomatic recovery does not reflect functional recovery in late life depression

The burden of psychiatric disorders is more dependent on the level of limitations in daily activities and relevant social contacts than on the actual severity of the psychiatric symptoms.[166] Functional recovery should therefore be an additional treatment target along with symptomatic recovery. We have studied the longitudinal course of functioning in late-life depression and searched for determinants of functional improvement over time. By combining symptomatic and functional recovery in the analyses, we showed that symptomatic recovery of late -life depression does not parallel functional recovery. Functional limitations improve only minimally after the remission of depressive symptoms (chapter 5), and functional recovery is only achieved by about one fifth of depressed older patients (chapter 6).

We do not know to what extent pre-existing functional limitations, caused by age-related factors, contribute to this unfavorable course. We assume that depression itself is a contributor to this outcome, because functional deficits also often remain in younger, somatically healthy depressed adults, even among patients who achieve symptomatic remission.[168] However, among younger depressed patients functional improvement is more directly associated with a reduction in depressive symptoms.[255] This suggests that depression itself causes persistent functional impairment in subgroups, irrespective of age.

Two important determinants of functional recovery are relevant in geriatric psychiatry: depression itself (also relevant for younger patients as described above) and somatic morbidity. We found that a higher number of chronic diseases was associated with non-recovery of functional limitation (see chapter 5 and 6). This is likely to be more specific for old age, because in old age, comorbidity with somatic diseases is more prominent than at younger ages.[165] In the NESDO study, a higher number of comorbid somatic diseases was associated with a poor course of late-life depression.[2,256] Moreover, a quarter of the sample could be classified as physically frail[225] which was also associated with a detrimental course of the depressive disorder.[169] Depression moderates the level of functional impairment associated with many somatic diseases, including cardiac disease, morbus Parkinson, and mild cognitive impairment.[188,257,258] These findings would suggest that improving depression will also improve the level of functional impairment, albeit not to the level of healthy older persons (as found in chapter 5). However, the chronicity of depressive symptoms in the face of multimorbidity and frailty may also point to over-detection of depression, as it has been argued that depressive symptoms are simply a sign or epiphenomenon of these underlying conditions.[259]

In conclusion, we found that functional status remains impaired in most of our subjects at the two year follow-up and that this is associated with more somatic illnesses. On

the other hand, we also found a group that was rather robust but nevertheless severely depressed and functionally impaired at baseline. Interestingly, this group showed the most favorable course in functional as well as symptomatic recovery (chapter 6). For future studies it would be interesting to separate these two groups; the old, frail with high levels of functional limitations versus the younger and fit/robust, with severe depressive disorders.

Furthermore, single-intervention anti-depressant treatment is apparently not enough to achieve functional recovery for a large group of patients. For optimal functional recovery, integrated care that includes the treatment of multiple comorbid medical and social problems simultaneously is needed. This type of treatment aligns with the multifactorial origin of (functional) impairment.

## Towards integrated care with a focus on functioning

The multifactorial origin of impairment in the older and frail depressed population stresses the need for a view that is broader than just the disease-centered approach. A focus on health and functioning as key outcomes seems to be more appropriate. Only 14 studies have examined which interventions may be relevant to improve functional recovery in late-life depression (Chapter 7). The evidence points towards collaborative care programs in particular, to increase the level of functioning of older people with depression.

Collaborative care studies were conducted in the early 1990s in the USA.[260] These models of integrated care are designed to promote collaboration between primary care providers and mental health specialists to improve access, planning, quality, and outcomes and treatment of depressed older adults. The studies included in our review were effective in improving functional limitations, and case management conducted mainly by specialized nurses was a common feature. Unfortunately, we could not determine which treatment components precisely predict functional improvement in these studies. In our opinion, however, it may not be specific interventions, but the personalized integrated care plan. Future studies into collaborative care should conduct a 'complex-intervention-studies approach' in order to disentangle the effects of the components of the intervention.[261]

The PRISM-e study showed that for major depression, reduction in symptom severity was higher for those randomly assigned to the enhanced specialty referral group in comparison with integrated care in primary care, whereas change in functioning did not differ across the two care models.[262] This may suggest that for major depression, treatment in specialized care is still indicated (according to psychiatric guidelines), but it needs more personalized care management within integrated care to improve functioning in collaboration with primary care. Translating this to the current Dutch organization of healthcare, where investments have been made in primary care to enable depression

treatment, in the next step, a focus on the collaboration of mental health institutions and primary care is needed.

This integrated approach to treat depressive disorder by incorporating strategies to simultaneously target comorbid somatic diseases, functional impairment and taking personal preferences and strength and weaknesses into account, is nothing new.[263] The paradigm shift from a biomedical model towards a more inclusive definition of health has been accomplished in the past decades and resulted in varies theoretical concepts like the ICF,[4] the "positive health" definition[202] and the positive psychology trend in mental health care.[264,265]

The concept of the International Classification of Functioning, Disability and Health (ICF) was reported to be useful in guiding clinical assessment and providing a comprehensive understanding of health and functioning from the first-person perspective. It considers a wide range of domains of functioning, which is particularly relevant for complex conditions.[125] Another proposal that takes a broader look at health-outcomes, is the "dynamic concept of health" by Huber et al.[202] She defines health as "the ability to adapt and to self-manage in the light of social, physical, and emotional challenges". This broad perception, which is captured in six domains (bodily functions, mental functions and perception, spiritual dimension, quality of life, social and societal participation and daily function) still requires further operationalization for clinical practice. It could result in a new clinical practice where patients are involved in making shared decisions based on the different health dimensions. This would result in improvements in the 'ability to cope', 'resilience' and 'self-management', as well as in better physical and mental health, in functioning in the various dimensions, and/or in health-related quality of life.

Since depressed older patients are a highly heterogeneous group with respect to underlying risk factors, comorbidities and consequences, integrated personalized care will optimize daily functioning (Chapter 7). In our study, patients with neither symptomatic remission nor functional recovery were characterized by a higher somatic disease burden, anxiety, and low sense of mastery. For these patients, geriatric rehabilitation should be considered as one of the core components of integrated care. And, according to our results in chapter 2 and 6, from a psychosocial perspective, it might be relevant to incorporate interventions with focus on a sense of mastery and anxiety. This approach provides the opportunity to add to the currently available anti-depressant treatment interventions, and to improve the success rate of anti-depressant therapy. By extending psychiatric symptom counts as a treatment outcome with functional outcomes, treatment outcomes are measured in a way that is closed to the patient's definition of a successful treatment.

Nevertheless, integrated care is not yet mainstream in everyday practice and scientific research. Organizational, financial, and technical hurdles need to be overcome for a solid reorganization from disease management towards integrated network health-care.[266]

Partnerships across traditional organizational and professional boundaries are needed. In an integrated system these partnerships can pass through the boundaries of the 'cure' and 'care' sector to provide a real continuum of care.[267] In the case of depression in older adults, this involves a reassessment of the role of specialized mental healthcare. Instead of delivering treatment from isolated outpatient psychiatric clinics, the system moves towards following the individual patient with his/her individual needs, in partnership with primary care and other care providers, in a network around the patient. In this scenario, mental health nurses could play an important role in the maintenance of symptomatic and functional recovery and by serving as case-managers between the mental health system and the other members in the network of the individual patient to optimize functional recovery.

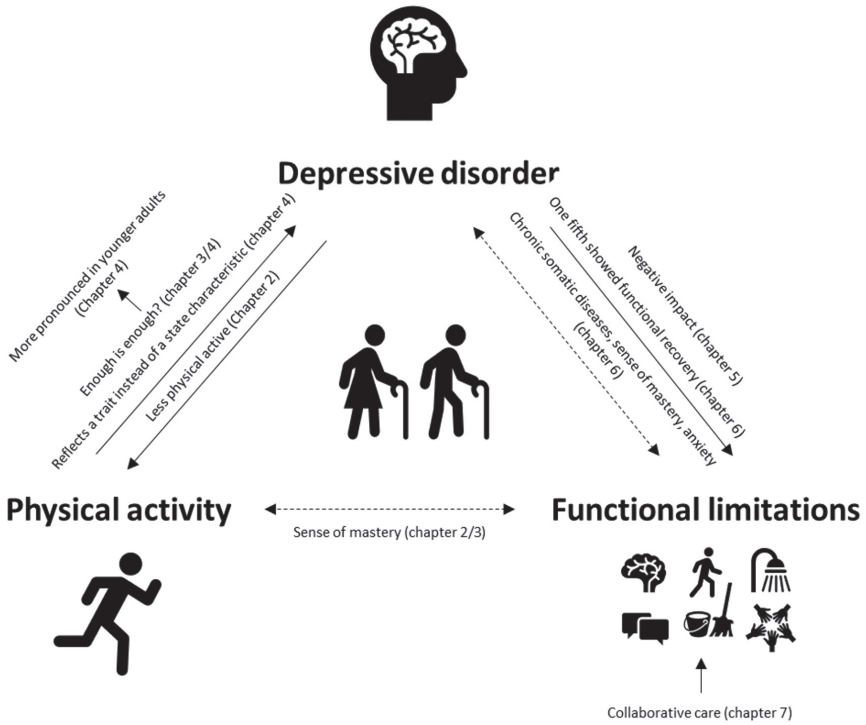



**Figure 1:** Relations found in this thesis

## Methodological considerations

The empirical findings in this thesis are based primarily on data from the Netherlands Study of Depression in Older persons (NESDO). In chapter 4, this data was augmented with data on depressed younger patients participating in the Netherlands Study of Depression and Anxiety (NESDA). Clinical cohort studies have several strengths and limitations. We will discuss the following aspects of these studies, which should be taken into account when weighing the outcome of this thesis: the definition of depression, the use of self-report questionnaires, especially in the assessment of physical activity and functional impairment, and finally the black box of interventions patients have received.

### Case definition of depression

The main subject of our studies was depression in later life. NESDO provides a large sample of older persons with depression. To include a broad range of depression severity, subjects were recruited from in primary care as well as (in- and outpatient) specialized mental health care. After recruitment, the depression diagnosis was confirmed by trained research assistants using the CIDI. The 378 subjects included depressed participants in the NESDO study experiencing a current DSM-IV classification of minor depression (5.6%) or major depressive disorder (95%), of which 26.5 % presented comorbid dysthymia. In this thesis, all analyzed samples included all depression diagnoses. In both samples (NESDA and NESDO), current psychiatric diagnosis was defined by a recency of 6 months. In the cross-sectional study (chapter 2), we selected only depressed cases who also met the criteria for a depressive disorder in the past month, while the level of activity was assessed over the previous week. This led to a more valid comparison of physical activity (since recent remission may already have increased the level of physical activity in previous week), but also to a smaller sample due to the exclusion of 72 participants. Based on the results in chapter 4, however, including all patients would not have biased the results, because physical activity appeared to be merely a trait characteristic. In the chapters that use longitudinal data, the importance of recency was considered to be less important than the opportunity to include as many as possible participants with follow up data. Moreover, by including all depressed patients using the past 6-month definition, we followed the a-priori definition of depression of NESDO and NESDA. Since physical activity appeared to remain stable over time and change in physical activity was not associated with remission of the depressive disorder at two-year follow-up, it is unlikely that these differences in recency affected the results.

One of the strong points of our dataset is that, in addition to the formal depression diagnosis, we also had measures on depression symptom severity, such as the IDS scores. The results on these scores show that we did include participants with a broad range of severity of depressive symptoms,[57] which reflects clinical practice. We were also

able to analyze the bidirectional relations between various depression characteristics in relation with physical activity and functional limitations.

## Outcome measurements

One of the strengths of observational cohort studies, especially NESDO and NESDA, is the opportunity to measure a plethora of data. This enabled us to study determinants of physical activity and functional limitations in late-life depression from a biopsychosocial perspective over time. We were nevertheless bound to the questionnaires used in NESDO. Physical activity was measured with the International Physical Activity Questionnaire (IPAQ) and functional limitations with the WHODAS 2.0, both self-report questionnaires. This section will cover usability and the cons regarding the use of our two major outcome measurements.

*Physical activity* – Physical activity was measured with the IPAQ. The IPAQ is a well-accepted instrument that has been validated in various subpopulations around the world.[77] Compared to other self-reported physical activity questionnaires, the IPAQ is one of the questionnaires with the most acceptable psychometric properties.[105] Reliability studies have shown that the IPAQ can be used in studies with repeated measurements, although the true magnitude of the change over time, if any, may not be accurate.[133] Results, especially in older adults, are mixed. For example, the IPAQ had poor concurrent validity and only categorized physical behavior correctly in 2% of older cases.[268]

Compared to the measurement of physical activity through the use of wearables, the IPAQ tends to overestimate the amount of physical activity in (healthy) older people.[269] Kowalski et al.[270] found only a moderate correlation between objective and self-reported physical activity in older adults (r=0.38). These results, however, are difficult to extrapolate to older persons with depression, because negative cognitions could downgrade this perception and cognitive problems could preclude a valid judgement even more.[271] Schuch et al.[272] found that the total time spent on physical activity was significantly higher with the use of objective measurements than with self-reported measurements in adults with depression. This suggests an underestimation of physical activity in depression, in contrast to the overestimation found among non-depressed persons. In our study, however, self-reported physical activity hardly changed over two years in an initially depressed group, and this was not influenced by remission of depression or by age (Chapter 4). In line with our self-report measurements, objectively measured physical activity studies also showed that depressed patients are less physically active in comparison to their non-depressed counterparts.[114]

In conclusion, it is evident that self-reported physical activity questionnaires measure the perception of one's own activity instead of the actual amount of activity. However,

wearables were not in widespread use at the start of NESDO. The increasingly available and affordable accelerometry devices would therefore be a logical addition in future research.[273,274] The results on the difference in perception (questionnaire) and the actual amount of activity (accelerometry) would therefore provide valuable information to boost (or develop) motivational interventions for lifestyle change as part of treatment.

*Functional limitations* - A recent systematic review on the assessment of the instrumental activities of daily living (IADL), social functioning, and general functioning showed that the large majority of instruments have not been validated in patients suffering from late-life depression.[240,242] Based on their findings, these researchers developed an algorithm to select functional assessment instruments in late-life depression for researchers and clinicians. With regard to the assessment of general functioning, the WHODAS 2.0 and the Late-Life Function and Disability Instrument (LLFDI) were recommended for research and clinical use. The LLFDI has more robust evidence for this subgroup, but was considered the second choice because the LLFDI requires more training and expertise to use. The LLFDI could therefore be used for researchers assessing functioning in late-life depression as a primary outcome, whereas the WHODAS 2.0 is the best alternative as a secondary outcome or supplemental part of their study.

Worldwide the WHODAS 2.0 is well-known and used in research and daily practice across all age groups.[275] In 2014, the American Psychiatric Association added the WHODAS 2.0 to the DSM-5 clinical classification to replace the General Assessment of Functioning (GAF) score. Despite the fact that work-related items were omitted for the NESDO study in order to optimize the sensitivity for change in functioning in retired older adults, results showed little change in WHODAS 2.0 total scores over time (chapter 5 and 6). To detect subtle changes, more research is needed in analyzing subscales, as was done in chapter 5. Unfortunately, due to skewed distribution of subscale scores (high frequency of null scores), this was not possible in the GMM analysis in chapter 6.

## Longitudinal observational study

The strength of this thesis is the opportunity to use the longitudinal data of the NESDO and NESDA. This allowed us to look at changes over time in chapters 3-6 and draw cause and consequence conclusions. The NESDO and NESDA were observational studies in which no restrictions were imposed on regular clinical care. Since the majority of patients were recruited after referral to specialized mental health care, most subjects have definitely received some form of treatment. Although the use of medication (including antidepressants and other psychotropic drugs) was available at baseline and two-year follow-up, it was not possible to assess the effect and appropriateness of these and other interventions on the course of the depressive disorder. First of all, at baseline it was not known whether patients had previously received anti-depressant

medication for a prolonged period (e.g. referred for treatment resistance) or were recently switched to these drugs. Furthermore, no data were available on the duration of use, dosage regimes and switches during the two-years of follow-up. Information on the other interventions, especially psychotherapy or interventions aimed at improving lifestyle, such as food and activity-habits, would be very interesting, but were not available for our groups, so we could only speculate as to the effect of these interventions. Nonetheless, in the Netherlands we have evidence-based guidelines for the treatment of depression, including late-life depression, and empirical studies have shown that adherence to these guidelines is quite good.[276] If true in our sample, we must conclude that the overall results of these interventions on the clinical course of depression were rather disappointing. However, the actual nature of these interventions remains a 'black box', as is the case in many observational studies similar to ours.

The meager results of treatment and the predominantly poor outcome after two and six years in our NESDO group could reflect the inherent problems of old-age psychiatry.[165] Most depressed subjects had somatic co-morbidity. In addition to depression, a range of other, somatic and cognitive/degenerative problems are involved, all with a negative impact on outcomes. This is also reflected in the rather large numbers of drop-outs at follow up, due to death (6.8% after 2 years, 16.4% after 6 years) and inability to continue participation (9.7% after 2 years, 11,5% after 6 years).[2,16] Participants lost to follow up were more severely depressed at baseline and had more functional limitations than the participants that were included in the analytical samples, suggesting that the most severely impaired persons were not followed-up. This may have biased our results towards an underestimation of the association that was found between depression and functional limitations. Furthermore, our study did not assess pre-morbid levels of functioning. We therefore cannot take a possible pre-existing vulnerability into account.

## Clinical implications

In the previous paragraphs, much is said about the implications of our results for clinical practice and research. It is clear that treatment and care for patients with late-life depression is complex and demands efforts from multiple disciplines. Future research should aim to indicate what works for whom. The starting point of this thesis was to contribute to the body of knowledge on the interrelationship between physical activity, functional recovery, and depressive disorder. Nurses play a major role in interventions aimed at these daily activities and functional recovery. The acquired knowledge could help to develop more targeted and nurse-led interventions. Therefore, in this last section, we will focus on the implications of this thesis for clinical care and research from the perspective of the nursing professionals.

With regard to physical activity, the challenge is to nudge patients towards a long term, sustainable behavioral change with high adherence. Based on this thesis, we can assume that enough is enough (chapters 3 and 4). Patients with low daily physical activity, can therefore be motivated to increase their level to a personalized amount of sufficient physical activity. Integrating physical activity into daily routines is emerging as a promising alternative.[277] This is currently being studied in the PreventIT project, which addresses the different phases of adopting a healthier lifestyle.[278] Based on our results, for patients suffering from late-life depression, it is important to take into account determinants of physical activity such as a low sense of mastery and individual functional impairments. Extra attention is also needed with inpatients (chapter 2). Nurses are well educated and are in a position to encourage and assist patients to engage in daily physical activity. Since the level of physical activity is merely a trait instead of a state characteristic (chapter 4), there will be a group of patients who requires long-term encouragement and support to attain this goal.

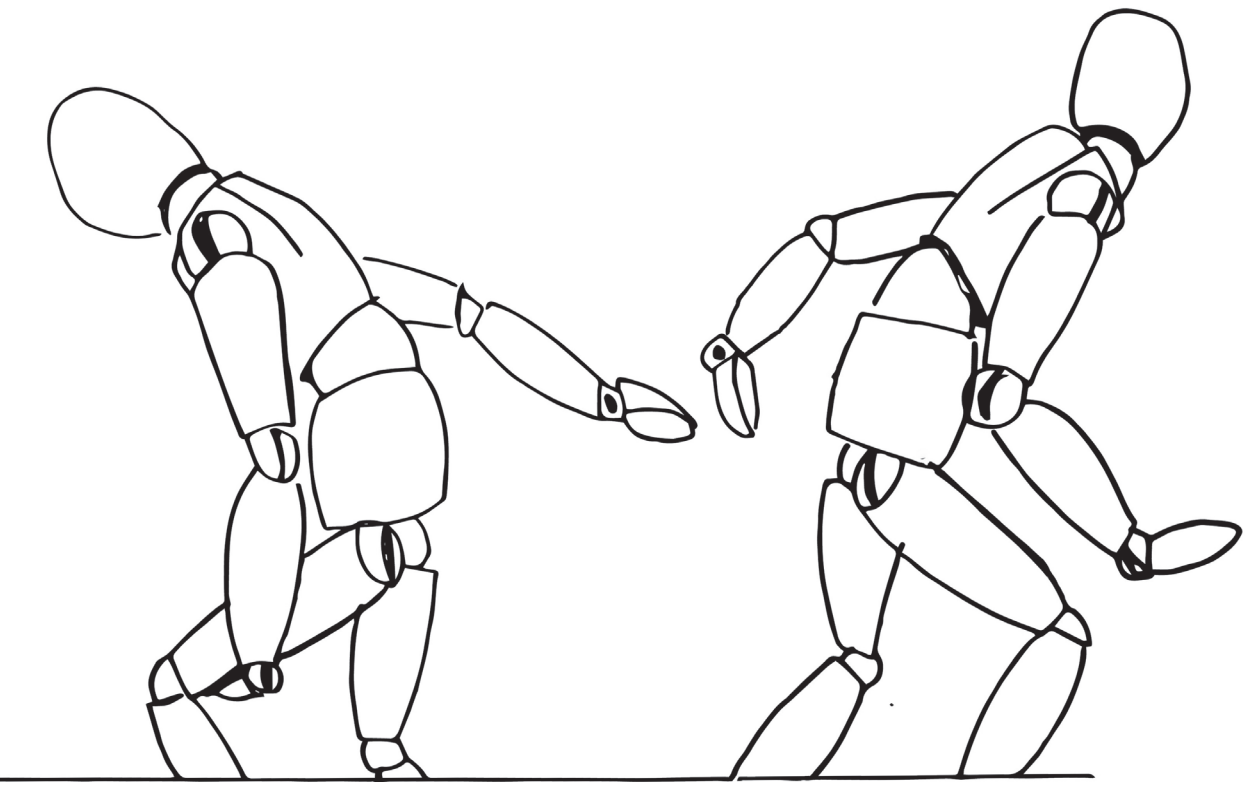
Concerning functional recovery, this thesis shows that only 2 out of 10 patients functionally recover, which can be interpreted as a large gap between symptomatic remission and functional recovery. One of the main conclusions of this thesis is therefore that increased focus on functional recovery as outcome in practice and research is inevitable. As mentioned earlier, functioning as an outcome is the key-factor for nursing professionals, who generally focus on the human as a person functioning in his or her daily life and not as someone with a specific disease. We therefore advocate, in line with Stallinga,[279] the adoption, practice and research of functioning as core outcome for the nursing profession. The ICF, with its acknowledgement of the interaction between people and their environments in health and disability, is a useful conceptual framework for clinical reasoning of nurses.[280-282]

A specific finding in this thesis, was that the most vulnerable and functionally-impaired depressed patients are characterized by high prevalence of chronic somatic diseases, a lower sense of mastery, and a higher level of anxiety (chapter 6). This vulnerability and comorbidity may have a negative impact on the self-management skills of patients. Self-management abilities, however, are important as older persons generally face a large network of caregivers due to their multimorbidity. The opportunity for optimizing functional recovery is a multidisciplinary collaboration of patient-centered, integrated care (chapter 7).

It is conceivable that these patients will benefit from the involvement of a nurse who takes on a crucial role in assisting the patient and their families in managing and coordinating care. This means helping the patients to define their unmet needs, assist them in goal setting, guide them in the information needed for informed shared decision making in treatment options, support them in their process and evaluate the effect of interventions

together. In such a way '*that the patient would perform unaided if they had the necessary strength, will, or knowledge and to do this in such a way as to help them gain full of partial independence as rapidly as possible'*.[3]

Being a nurse practitioner myself, I hope this thesis will stimulate and contribute the development of integrated care for depressed older persons beyond the borders of mental and somatic health care.



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